vertebrate homologs and Fam151 family members. Once again, studies of the worm nervous system have uncovered a new path for a growing field.

REFERENCES

Appel, F., Holm, J., Conscience, J.F., von Bohlen und Halbach, F., Faissner, A., James, P., and Schachner, M. (1995). J. Neurobiol. *28*, 297–312.

Dong, X., Liu, O.W., Howell, A.S., and Shen, K. (2013). Cell *155*, this issue, 296–307.

Jan, Y.N., and Jan, L.Y. (2010). Nat. Rev. Neurosci. *11*, 316–328.

Liu, O.W., and Shen, K. (2012). Nat. Neurosci. *15*, 57–63.

Parrish, J.Z., Emoto, K., Kim, M.D., and Jan, Y.N. (2007). Annu. Rev. Neurosci. *30*, 399–423.

Pocock, R., Bénard, C.Y., Shapiro, L., and Hobert, O. (2008). Mol. Cell. Neurosci. *37*, 56–68.

Salzberg, Y., Diaz-Balzac, C.A., Ramirez, N., Attreed, M., Tecle, E., Desbois, M., Kaprielian, Z., and Buelow, H.E. (2013). Cell *155*, this issue, 308–320.

Silletti, S., Mei, F., Sheppard, D., and Montgomery, A.M. (2000). J. Cell Biol. *149*, 1485–1502.

Remembrance of Cilia Past

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The primary cilium is thought to be disassembled prior to mitosis, freeing the centrosomes to participate in the mitotic spindle. In this issue, Paridaen et al. demonstrate that a remnant of the ciliary membrane remains attached to the mother centriole and is asymmetrically inherited in the developing neocortex.

Information about the state of a cell in one generation can be transmitted through cell division to the next generation, maintaining a form of cellular memory. These "memories" ultimately have a molecular basis, and asymmetric segregation of these molecular manifestations of cellular memory is an important part of asymmetric cell division. Such divisions are typical of stem cells, in which one cell retains the stem cell fate and the other differentiates into another cell type. The best-known examples of cellular memory mechanisms involve chromosomes, with their epigenetic markings that control how they are expressed. But in this issue, Paridaen et al. (2013) describe a cytoplasmic instantiation of cellular memory involving the centrosome and primary cilium.

"Cilium" is Latin for eyelash, and the primary cilium is a single, nonmotile eyelash-like structure that grows from the older of the two centrioles within a centrosome. The primary cilium was identified most clearly by electron microscopists in the 1950s and 60s, but its function was unknown, and in one of the great disappearing acts of 20th century cell biology, it fell from favor as a topic of study. However, the primary cilium has come back into vogue recently, as a result of genetic studies in mouse and humans that showed that it is an essential sensor for mechanical and chemical signals from the extracellular environment and is a signaling platform for several important signaling pathways (Garcia-Gonzalo and Reiter, 2012).

If the primary cilium is so important as a signaling hub, controlling which cells make a cilium and when they make it would be critical. In most animal cells, the primary cilium is disassembled prior to mitosis and is assembled again in G1 following division, and this cilium cycle is tied to the centriole cycle. Centrioles duplicate once per cell cycle (Nigg and Stearns, 2011) by a semiconservative mechanism that is superficially like that of DNA replication. In G1, each cell has a pair of centrioles—one newer, which was formed in the previous cell cycle, and one older, which was formed in some earlier cycle. The convention is to refer to the older as the mother centriole and the younger as the daughter. The mother centriole has specialized appendages at its distal end that allow it to interact with the plasma membrane and form a cilium. Depending on the cell type, the requirements for cilium formation are presence of a mother centriole with appendages, G1 cell-cycle stage, and, for maximum extent of ciliogenesis, a driver of quiescence such as serum starvation or contact inhibition. In a cycling cell, the centrioles duplicate at the entry into S phase such that two new daughter centrioles grow, each tightly apposed to one of the original centrioles. So, at this stage, there is an old mother and a new mother centriole, each with a daughter centriole. In most cells, the cilium is disassembled in S phase, and the two centriole pairs are free to associate with the mitotic spindle and then segregate to the two products of division (Figure 1).

Every cell division is asymmetric with respect to centrioles—one cell receives the old mother centriole, and the other receives the new mother centriole. These centrioles differ by age and potentially by history of cilium formation, i.e., the old mother may have made a cilium in a previous cell cycle, whereas the new mother has never made a cilium because it only matured and gained the required appendages in the current cycle. In both *Drosophila* and mammals, there are examples in which the centrioles are inherited asymmetrically with respect to cell fate (Habib et al., 2013; Januschke et al., 2013; Pelletier and Yamashita, 2012) but little evidence as yet that centrosomes bear determinants of cell fate. However, the intrinsic centriole asymmetry does have clear consequences for the timing of cilium formation after division: a mammalian cell that receives the old mother centriole in a division is able to assemble a primary cilium earlier than the cell receiving the new mother centriole, and this confers on the early cell the ability to respond to Sonic hedgehog signal, which requires a primary cilium (Anderson and Stearns, 2009). Similar results with respect to asynchrony of cilium formation and signaling responsiveness have also been found in vivo in mouse neuroepithelium (Piotrowska-Nitsche and Caspary, 2012).

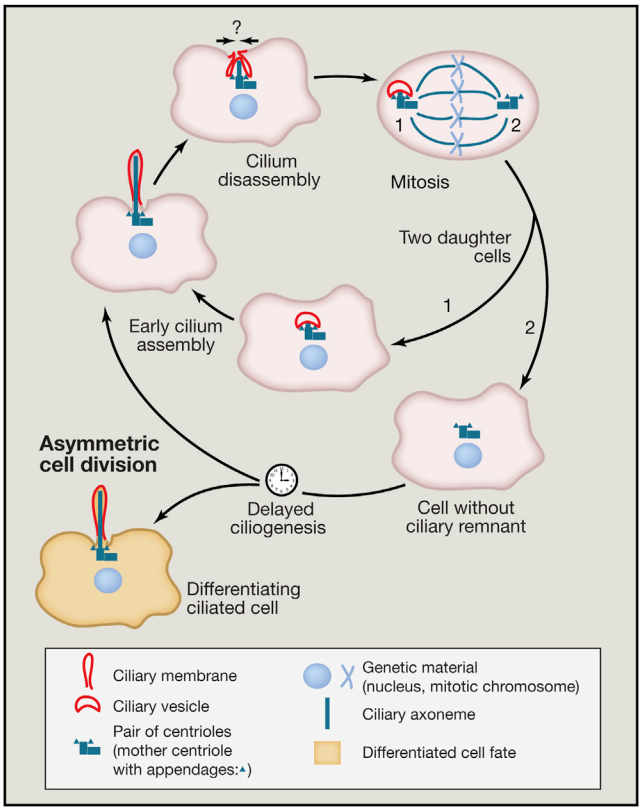

Figure 1. Inheritance of a Ciliary Membrane Remnant Underlies Asynchronous Primary Cilium Formation in Sister Cells

Prior to mitosis, the ciliary membrane (red) is retracted into the cell during cilium disassembly via an as yet unidentified mechanism. It stays attached to the older mother centriole in the form of a ciliary membrane remnant, or vesicle, throughout mitosis. The daughter cell that inherits the ciliary remnant (1) assembles the primary cilium earlier than its sister, which has to form a cilium de novo (2). In cases of asymmetric division, e.g., stem cells, the ciliary remnant is preferentially inherited by the daughter cell that retains the stem cell character, whereas its sister that lacks the ciliary remnant and that therefore assembles the primary cilium only later undergoes differentiation (yellow).

These results suggested the possibility that an old mother centriole's prior history of making a cilium was a cellular memory that could be passed on to the next generation. But what is the element that, like Proust's madeleine and tea and their invocation of his childhood memories, is able to invoke the memory of past cilium formation and speed its occurrence in the present? The results of Paridaen et al. (2013) beautifully demonstrate that the cell that inherits the old mother centriole in a division also inherits the cellular memory of that centriole having made a cilium previously, in the form a remnant of the ciliary membrane itself. The ciliary membrane is continuous with the plasma membrane but has a distinct lipid composition and is enriched in proteins involved in ciliary signaling pathways (Garcia-Gonzalo and Reiter, 2012). Most work on the cilium cycle has focused on assembly, the steps by which a centriole interacts with the plasma membrane and forms the ciliary membrane compartment, which then expands as the ciliary axoneme elongates. Paridaen et al. focus instead on disassembly and note that some markers of the ciliary membrane are retained at one of the two centrosomes in a dividing cell, even after the cilium has been disassembled. They then show by electron microscopy that this corresponds to a membrane vesicle associated with the distal end of the centriole. This suggests that cilium disassembly occurs by shortening of the ciliary axoneme, followed by internalization of the remaining axoneme and membrane by what could be considered to be an endocytosis event (Figure 1). Thus, the older mother centriole retains a vesicular remnant of the ciliary membrane. Remnants of the ciliary axoneme had been observed previously in mitotic cells (Rieder et al., 1979), but they were thought to be devoid of membrane, and the results of Paridaen et al. now demonstrate perdurance of the ciliary membrane compartment through cell division.

How might the presence of a ciliary membrane remnant on a centriole in mitosis affect cilium formation in G1 of the next cell cycle? Paridaen et al. show that the cell that receives the remnant-bearing centriole is able to assemble a primary cilium before its sister in division, providing a structural basis for the previously described correlation of centriole age with ciliary asynchrony (Anderson and Stearns, 2009). Remarkably, there have been many previous EM descriptions of a large vesicle associated with the distal end of centrioles prior to cilium assembly, dating to some of the earliest EM observations (Sorokin, 1962). The interpretation of these has been that they represent an intermediate step on the pathway and are formed by the capture of a vesicular membrane by the G1 centriole and the subsequent enlargement of that vesicle, followed by fusion of the ciliary vesicle with the plasma membrane (Garcia-Gonzalo and Reiter, 2012). However, the results of Paridaen et al. suggest a simpler model, wherein most observations of a centriole-associated ciliary vesicle are actually of a ciliary

remnant on a centriole that has previously made a cilium. Cilium assembly from such an experienced mother centriole would require only fusion of the cilium remnant with the plasma membrane, whereas a naive mother centriole might have to first establish an interaction with an internal membrane or directly with the plasma membrane before the cilium compartment is formed. The former might be expected to be faster than the latter, explaining the asynchrony in cilium formation.

What are the consequences of this centriolar asymmetry and ciliary asynchrony after cell division? Paridaen et al. show that in neural stem cells the older mother centriole and its associated ciliary remnant usually segregated to the stem cell in an asymmetric division and that the cell receiving the remnant made a cilium first and was responsive to Sonic hedgehog ligand. Interestingly, at late neurogenic stages of development, the internalized ciliary membrane was often not associated with the centriole, and such cells did not display the asynchronous cilium assembly phenotype. These results support the hypothesis that the intrinsic asymmetry of centriole age, present in all cell divisions, is used to confer specific phenotypes in asymmetric cell divisions, including a memory of the cellular history of elaborating a particular signaling apparatus, the primary cilium.

REFERENCES

Anderson, C.T., and Stearns, T. (2009). Curr. Biol. *19*, 1498–1502.

Garcia-Gonzalo, F.R., and Reiter, J.F. (2012). J. Cell Biol. *197*, 697–709.

Habib, S.J., Chen, B.C., Tsai, F.C., Anastassiadis, K., Meyer, T., Betzig, E., and Nusse, R. (2013). Science *339*, 1445–1448.

Januschke, J., Reina, J., Llamazares, S., Bertran, T., Rossi, F., Roig, J., and Gonzalez, C. (2013). Nat. Cell Biol. *15*, 241–248.

Nigg, E.A., and Stearns, T. (2011). Nat. Cell Biol. *13*, 1154–1160.

Paridaen, J.T.M.L., Wilsch-Bräuninger, M., and Huttner, W.B. (2013). Cell *155*, this issue, 333–344.

Pelletier, L., and Yamashita, Y.M. (2012). Curr. Opin. Cell Biol. *24*, 541–546.

Piotrowska-Nitsche, K., and Caspary, T. (2012). Cilia *1*, 6–16.

Rieder, C.L., Jensen, C.G., and Jensen, L.C. (1979). J. Ultrastruct. Res. *68*, 173–185.

Sorokin, S. (1962). J. Cell Biol. *15*, 363–377.